Differential Diagnosis of Distal Myopathies

The era of clinical molecular genetics has refined diagnosis and will hopefully lead to disease-modifying treatments.

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Distal myopathies comprise a rare and heterogeneous group of disorders that present with weakness of the distal muscles of the hands, feet, or both. The term distal myopathy is usually reserved for genetic disorders, although weakness of distal muscles is sometimes prominent in the acquired muscle diseases. In addition, prominent distal muscle weakness is also a feature of several of the most common inherited myopathies including myotonic muscular dystrophy type 1 (DM1) and facioscapulohumeral muscular dystrophy (FSHD). The first description of a distal myopathy was provided in a series of cases from 1885 through 1893. Detailed clinicopathologic study of these cases documented distal muscular atrophy—or peripheral muscular tabes—in the absence of nervous system involvement. The term distal myopathy was first mentioned in 1902 in a person with concurrent facial weakness, which may have been an early description of myotonic dystrophy type 1. In 1951, clinicopathologic findings were reported for an adult-onset autosomal dominant disorder with weakness of long extensors in the hand; 249 people from 72 Swedish families were affected. The molecular genetic era for distal myopathies began in 1995 with mapping of Laing’s distal myopathy to chromosome 14 and the later discovery of causative MYH7 mutations. The Gene Table of Neuromuscular Disorders now lists 18 gene disorders under the heading distal myopathies and recent comprehensive review has added another 7 gene disorders. This review highlights classic distal myopathies, including genetic and clinicopathologic aspects and other categories of genetic myopathy associated with distal weakness, and provides a brief review of the evaluation and care of people with these disorders.

**Evaluation**

For most cases, EMG is an important initial test to confirm the myopathic origin of weakness and search for other diagnostic clues. For example, identifying symptom onset, family history, and pattern of muscle involvement are key to guiding further diagnostic studies (Figure 1). In clinical practice, distal limb weakness of myopathic origin is uncommon and, therefore, other neuromuscular disorders must be considered, including motor neuron diseases and polyneuropathies. Hereditary motor neuropathies and Charcot–Marie–Tooth neuropathies are particularly important to consider in familial cases presenting with bilateral foot drop, hand weakness, or both. Clinical clues, including preserved foot muscle bulk in the setting of bilateral foot drop, preservation of intrinsic hand muscle function in the setting of prominent finger extensor weakness, and concurrent neck or proximal limb muscle weakness, suggest primary muscle disease rather than neuropathy.

For most cases, EMG is an important initial test to confirm myopathic origin of weakness that may also give other clues. For example, myotonic discharges implicate a myotonic dystrophy or, possibly, Pompe’s disease, and findings of fibrillations and positive sharp waves focus further testing on dystrophic myopathies. Creatine kinase (CK) values are helpful and may be normal or mildly elevated in most disorders, but highly elevated in dysferlinopathies and other muscular dystrophies.

Imaging upper and lower limb muscles with MRI provides valuable insight on patterns of involvement, especially if the clinical exam is limited (eg, in an individual who is obese). Muscle biopsy findings vary and may give valuable diagnostic clues or show only nonspecific or nondiagnostic changes (Figure 2). Some characteristic findings are dystrophic changes (eg, Miyoshi myopathy, ANOS-related myopathy), rimmed vacuoles (eg, GNE-related myopathy, myofibrillar myopathies), and fiber type disproportion (eg, Laing’s myopathy, congenital myopathies). Muscle immunohistochemistry is helpful in identifying deficient structural proteins in recessive dystrophies (eg, Miyoshi’s myopathy) or abnormal protein accumulation in myofibrillar myopathies (eg, DES-related myopathy). Muscle biopsy is not always needed, given availability of next-generation DNA testing, but may be important if DNA test results are negative or report only variants of uncertain significance.
Classic Distal Myopathies

Laing’s Myopathy

Laing’s myopathy is an early-onset disorder that begins with selective weakness of foot dorsiflexors and great toe extensors, followed by weakness of neck flexors and finger extensors, and, in some cases, progresses to facial and proximal limb muscle weakness. Levels of CK are normal or mildly elevated. Muscle histopathology varies to include mild nonspecific changes, congenital fiber type disproportion, cores and minicores, and dystrophic changes. Laing’s myopathy is an autosomal dominant disorder caused by MYH7 mutations affecting the β heavy chain of myosin.

Other MYH7-allelic disorders include skeletal myopathies (congenital myopathies, late-onset myopathies, myosin storage myopathy, scapuloperoneal myopathies) and cardiomyopathies (dilated, hypertrophic, and left ventricular noncompaction). There are 1,010 MYH7 mutations reported, spanning the globular head region and rod domains of myosin. Mutations in MYH7 are likely to impair development of a normal coiled structure impacting myosin dimerization, which is required to form the thick filament.

GNE Myopathy

GNE myopathy (Nonaka’s myopathy, distal myopathy with rimmed vacuoles, hereditary inclusion myopathy type 2) is a primary skeletal myopathy usually presenting in late adolescence and early adulthood with bilateral foot drop and steppage-pattern gait caused by anterior tibialis muscle weakness. Weakness progresses over years to ultimately involve hip flexors, shoulder girdle, and hand muscles. For most people, the quadriceps will be spared even in advanced disease. Loss of ambulation occurs 20 to 30 years after onset. Facial, oropharyngeal, cardiac, and respiratory muscles are usually spared with few exceptions. Levels of CK are mildly elevated, usually less than 5 times the upper normal limit. Characteristic muscle histopathology features include rimmed vacuoles and filamentous inclusions. GNE myopathy is an autosomal recessive disorder caused by GNE mutations affecting UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase. There have been 224 mutations reported in GNE gene with founder mutations in individuals of Japanese and Middle Eastern ancestry. The pathophysiology is not entirely known but hypo-sialylation of muscle glycans is believed to play a major role. Extended-release sialic acid showed no benefit over placebo in improving muscle strength or function, however.

Miyoshi’s Myopathy

Miyoshi’s myopathy is a primary disorder of skeletal muscle usually presenting with the triad of onset before age 20 years, early involvement of posterior foreleg muscles, and markedly elevated CK levels (20-50 times normal upper limit). Progression is slow but relentless, eventually involving proximal muscles, and leading to wheelchair dependency 10 to 20 years after symptom onset. In addition to myopathic recruitment patterns, EMG shows fibrillations and positive sharp waves in resting muscle. Muscle biopsy shows varying degrees of dystrophic change including myo-
Figure 2. Photo examples of clinical exam and muscle histopathology in patients with hereditary distal myopathies—including finger and wrist extensor weakness in Laing myopathy (A), marked gastrocnemius atrophy in Miyoshi myopathy (B), centralized nuclei in centronuclear myopathy due to DMN2 mutation (H&E) (C), congenital fiber type disproportion in Laing myopathy (NADH-TR) (D), rimmed vacuoles in GNE-related myopathy (Gomori trichrome) (E), and increased immunoreactivity to desmin in DES-related distal myopathy (F).

fiber necrosis and increased connective tissue. Immunostains show absent dysferlin. Diagnosis is confirmed with DNA testing that shows homozygous or compound heterozygous DYSF mutations. There are 599 reported mutations of DYSF. Other allelic disorders include limb-girdle muscular dystrophy (LGMD) type 2B and distal myopathy with anterior or foreleg-onset weakness. The DYSF gene encodes dysferlin, which is located in the muscle membrane and plays a major role in sarcolemmal repair.

Udd’s Myopathy
Udd’s myopathy (tibial muscular dystrophy) is a primary skeletal myopathy causing weakness of ankle dorsiflexors leading to bilateral foot drop and steppage-pattern gait usually beginning in adults more than age 35. Udd’s myopathy progresses slowly, remains limited to foot and toe extensors, and is so insidious that some may remain unnoticed even in later years. Levels of CK are normal or mildly increased. Muscle biopsy shows nonspecific myopathic changes with dystrophic changes and rimmed vacuoles in some cases. Udd’s myopathy is an autosomal dominant disorder first described in Finnish individuals; all reported cases with a founder variant in TTN associated with a unique 11-bp deletion/insertion that changes 4 amino acid residues in exon Mex6. Other pathogenic variants have been described in non-Finnish families. Other TTN-related allelic disorders include young adult-onset recessive distal titinopathy, LGMD type 2J, hereditary myopathy with early respiratory failure, early-onset myopathy with fatal cardiomyopathy, congenital centronuclear myopathy, multi-minicore disease with cardiomyopathy, and familial hypertrophic and dilated cardiomyopathies. There are 352 mutations reported in TTN, which encodes the giant sarcomeric protein, titin that spans the Z-disc to the M-band. How TTN mutations cause myopathy is not entirely clear, but likely involves disruption of the scaffolding and elastic recoiling properties of titin in its support of the sarcomere.

Welander’s Myopathy
Welander’s myopathy is a primary skeletal myopathy presenting in adulthood with distal upper extremity weakness, typically affecting wrist and finger extensors at onset with later involvement of the intrinsic hand and distal leg
Progression is typically slow with most remaining ambulatory. Levels of CK are normal or mildly increased. Muscle biopsy shows myopathic changes and rimmed vacuoles. The causative gene in Welander’s myopathy is TIA1. The disorder is found predominantly in Sweden and parts of Finland with a founder mutation (E384K) common to all cases. Other allelic disorders due to TIA1 mutations include frontotemporal dementia and amyotrophic lateral sclerosis. The coexistence of the TIA1 variant (N357S) combined with a pathogenic variant in SQSTM1 (digenic inheritance) causes a late-onset myopathy with involvement of the finger extensors and ankle dorsiflexors. The mechanism of muscle dysfunction in Welander’s myopathy is uncertain; however, reduced TIA1 activity may result in decreased response to oxidative stress, possibly leading to muscle cell atrophy.

Markesbery-Griggs Myopathy

Markesbery-Griggs myopathy (myofibrillar myopathy type 4) is an autosomal dominant, late-onset disorder usually presenting with bilateral anterior foreleg weakness and foot drop. Later, individuals develop weakness of finger and wrist extensors, and proximal leg weakness leading to loss of ambulatory function after 10 to 20 years of progression. Concurrent cardiomyopathy and conduction system dysfunction in Welander’s myopathy is uncertain; however, the congenital myopathies into 5 major groups: nemaline, core, centronuclear, myosin storage, and congenital fiber type disproportion. Distal-onset weakness has been associated with several congenital myopathy disorders, including ACTA1, MYH7, RYR1, and NEB gene disorders.

Complex Neuromyopathy Disorders

Advances in DNA testing have facilitated discovery of several complex neuromyopathies and multisystem proteinopathies that combine multiple phenotypes including distal myopathy, hereditary motor neuropathy, Charcot–Marie–Tooth neuropathy, amyotrophic lateral sclerosis, frontotemporal dementia, and Paget’s disease of bone. Several genes are implicated in these rare disorders including DNM2, HNRNPA1, HNRNPA2, HSPB1, HSPB8, MATR3, SQSTM1, TIA, and VCP.

Muscular Dystrophies and Other Inherited Myopathies

Some more common muscular dystrophies (eg, myotonic dystrophy type 1 and FSHD) may present with distal limb muscle weakness. Other muscular dystrophies and inherited myopathies presenting with distal weakness include the dysferlinopathies, myotilinopathies, anoctaminopathy, caveolinopathies, and telethoniopathies.

Care and Treatment

No effective disease-modifying treatments for distal myopathies exist yet. The hope is that some or all of the potential therapies under development, including oligonucleotide-based therapies, small molecule therapies, genome editing, gene replacement, and stem cell therapy, will provide future benefit to people with these progressive neuromuscular disorders. Until then, disease monitoring, rehabilitative support, physical therapy and exercise programs, and symptomatic treatments are the mainstay of care for individuals with distal myopathy. This author recommends referral to neuromuscular centers with experience in diagnosis and care for genetic neuromuscular disorders.
Periodic assessments by a team of providers—including neuromuscular neurologists, physical medicine specialists, cardiologists, pulmonologists, sleep disorder specialists, neuropsychologists, physical and occupational therapists, speech and language pathologists, dietitians, social workers, and respiratory therapists help maximize functional abilities, monitor for potential cardiopulmonary complications, navigate insurance and home care issues, provide psychosocial counseling, and, ultimately, improve the quality of life for individuals with distal myopathy and caregivers. In the US, Muscular Dystrophy Association (MDA) Care Centers are particularly suited for such care.